

## REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-6, 9, 11, 20-21, 28-33, 37-55, 59-63 and 68-70 are pending. Non-elected claims 7-8 and 64-67 were withdrawn from consideration by the Examiner. Applicants cancel the nonelected claims without prejudice to future prosecution of that subject matter. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

Claims 2-3, 5-6, 9 and 33 were withdrawn from consideration by the Examiner as allegedly being drawn to nonelected inventions or species. It was further alleged that there is no allowable generic or linking claim. Applicants request rejoinder of claims 2-3, 5-6, 9 and 33. Claim 9 further defines the amino acid sequence of the polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of ApoE-CTD or an amino acid sequence of a part thereof. The Action mailed October 10, 2007 required election of an antibody species including sequences of the three heavy chain CDRs and the three light chain CDRs, but it did not require the election of a polypeptide species. Thus, rejoinder of claim 9 which recites the amino acid sequence of the polypeptide is requested.

Claim 33 recites an antibody or antibody fragment which comprises the heavy chain sequence shown in SEQ ID NO: 40 and the light chain sequence shown in SEQ ID NO: 518 and/or 519 or the light chain sequence shown in SEQ ID NO: 520 and/or 521. SEQ ID NO: 40 is a heavy chain variable region sequence that comprises the heavy chain CDR sequences shown in SEQ ID NOS: 24 to 26 (see Table 8 at page 94 of the specification and Annex 1). SEQ ID NOS: 518 and 520 are light chain variable region sequences that each comprise the light chain CDR sequences shown in SEQ ID NOS: 33 to 35 (see Tables 8 and 21, Example 33 at page 80 of the specification, and Annex 1). SEQ ID NOS: 519 and 521 are light chain constant region sequences (see Table 21 at page 123 of the specification). Therefore, claim 33 is directed to the elected antibody species and rejoinder of this claim is requested.

Claim 1 is amended to recite that it:

- (i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof;
- (ii) binds to human plaques; and
- (iii) comprises:
  - (a) a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 26, or an affinity matured variant thereof;
  - (b) a heavy chain CDR2 region comprising the sequence shown in SEQ ID NO: 25, or an affinity matured variant thereof;
  - (c) a heavy chain CDR1 region comprising the sequence shown in SEQ ID NO: 24, or an affinity matured variant thereof;
  - (d) a light chain CDR3 region comprising the sequence shown in SEQ ID NO: 35, or an affinity matured variant thereof;
  - (e) a light chain CDR2 region comprising the sequence shown in SEQ ID NO: 34, or an affinity matured variant thereof; and
  - (f) a light chain CDR1 region comprising the sequence shown in SEQ ID NO: 33, or an affinity matured variant thereof.

Claim 1 is a generic claim that links the species of claims 2-3 and 5-6. Claim 1 recites an antibody having the CDR sequences shown in SEQ ID NOS: 24 to 26 and 33 to 35 and variants thereof. Several variants of these sequences are disclosed in Applicants' specification which also provides a clear description of further variants and how the skilled artisan may make and/or use them. The CDR sequences set out in claims 2-3 and 5-6 are all affinity matured variants of the CDR3 sequence shown in SEQ ID NO: 26. Therefore, rejoinder of claims 2-3 and 5-6 is requested because claim 1 is a generic linking claim.

Further, under the Commissioner's Notice of March 26, 1996 (1184 OG 86) implementing the Federal Circuit's decisions of *In re Ochiai*, 37 USPQ2d 1127 (1995) and *In re Brouwer*, 37 USPQ2d 1663 (1996), Applicants request rejoinder of the non-elected method claims upon an indication that an elected product claim is allowable.

*Specification/Claim Objections*

The brief description of the drawings is amended to refer to the different parts of Figs. 1-2 and 9. Withdrawal of the objection to the specification is requested.

The Examiner objected to claims 4 and 37-41 as being of allegedly improper dependent form. Claim 1 is amended as described above. In accordance thereto, the heavy chain CDR3 region and the light chain CDR1, CDR2 and CDR3 regions defined in claims 4 and 37-39 are affinity matured variants of the heavy chain CDR3 region and the light chain CDR1, CDR2 and CDR3 regions having the sequences set out in claim 1. Annex 1 shows the alignments of each of the CDR sequences recited in claim 1 with the affinity matured variant CDR sequences recited in the dependent claims.

The heavy chain sequence defined in claim 40 and the light chain sequences defined in claim 41 are specific heavy chain variable region and light chain variable region sequences that comprise the heavy chain and the light chain CDR1, CDR2 and CDR3 sequences, or affinity matured variants of those sequences, as set out in claim 1. Annex 1 illustrates where the CDR sequences recited in claim 1, or affinity matured variants thereof, occur within the heavy chain and light chain variable region sequences recited in claims 40 and 41.

Therefore, claims 4 and 37-41 are in proper dependent form as they further limit the subject matter of a previous claim. Withdrawal of the claim objections is requested.

*35 U.S.C. 112 – Definiteness*

Claims 54-55 were rejected under Section 112, second paragraph, as being allegedly “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Applicants traverse.

Claim 1 as amended specifies a human, humanised or chimeric antibody. Claim 54 requires a humanised antibody of claim 1. Claim 55 requires a chimeric antibody of claim 1. Claims 54 and 55 are therefore clear and definite.

Applicants request withdrawal of the Section 112, second paragraph, rejection.

*35 U.S.C. 112 – Enablement*

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1, 4, 11, 20-21, 28-32, 37-41, 51-55, 59-60 and 68 were rejected because “the specification, while being enabling for a human antibody or antibody fragment which binds to the C-terminal domain of ApoE and comprises either a heavy chain and a light chain or three CDRs of the heavy chain and three CDRs of the light chain,” allegedly “does not reasonably provide enablement for an antibody comprising fewer than six CDRs. It was further alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Applicant traverses.

Claim 1 is amended to recite: “An isolated human, humanised or chimeric antibody or antibody fragment, which antibody or fragment:

- (i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof;
- (ii) binds to human plaques; and
- (iii) comprises:
  - (a) a heavy chain CDR3 region comprising the sequence shown in SEQ ID NO: 26, or an affinity matured variant thereof;
  - (b) a heavy chain CDR2 region comprising the sequence shown in SEQ ID NO: 25, or an affinity matured variant thereof;
  - (c) a heavy chain CDR1 region comprising the sequence shown in SEQ ID NO: 24, or an affinity matured variant thereof;

- (d) a light chain CDR3 region comprising the sequence shown in SEQ ID NO: 35, or an affinity matured variant thereof;
- (e) a light chain CDR2 region comprising the sequence shown in SEQ ID NO: 34, or an affinity matured variant thereof; and
- (f) a light chain CDR1 region comprising the sequence shown in SEQ ID NO: 33, or an affinity matured variant thereof.”

Claim 1 as amended thus requires that the antibody comprises six CDRs.

The present specification discloses several antibodies that bind to the C-terminal domain of ApoE. Applicants identified an antibody having the heavy chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 24, 25 and 26, respectively and light chain CDR1, CDR2 and CDR3 sequences shown in SEQ ID NOS: 33, 34 and 35, respectively, that binds to the C-terminal domain of ApoE. This antibody is referred to in their specification as “807A-M0028-B02” (see Table 8 at page 94, line 2). Applicants also produced affinity matured variants of this antibody, which variants retain the ability to bind to the C-terminal domain of ApoE. The CDR sequences of these affinity matured variants are described in Table 38 at page 144 of their specification and the sequences of selected variants are shown in Tables 43 and 44 at pages 149-150 of their specification.

Applicants’ specification also discloses methods that may be used to obtain affinity matured variants (see page 28, line 2, to page 30, line 20) and describes how the affinity matured variants of an antibody having the heavy chain CDR sequences shown in SEQ ID NOS: 24 to 26 and the light chain CDRs shown in SEQ ID NOS: 33 to 35 were obtained (see Examples 38 and 39 at pages 82-89).

The present specification thus provides sufficient disclosure that would enable the skilled artisan to make and/or use not only an antibody having the CDR sequences of SEQ ID NOS: 24 to 26 and the light chain CDR sequences of SEQ ID NOS: 33 to 35, but also to make and/or use affinity matured variants of these sequences that bind to the C-terminal domain of ApoE and to human plaques.

Therefore, Applicants' specification enables a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use their invention commensurate in scope with the present claims.

Claim 60 was rejected as allegedly "failing to comply with the enablement requirement." It was further alleged that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse.

Claim 60 recites a method of treating a subject suffering from an amyloid disorder comprising administering to said subject a therapeutically effective amount of an antibody or antibody fragment that binds to the C-terminal domain of ApoE.

The Examiner acknowledges that the specification discloses a mouse model of Alzheimer's disease in which the presence of ApoE in brain plaques can be detected with an antibody that binds to the C-terminal domain of ApoE, but she objects that Applicants' specification does not disclose whether the binding of the antibody results in the removal of existing plaques or the inhibition of formation of new plaques.

Huang *et al* teach that C-terminal truncated forms of ApoE are present to a greater extent in brains of subjects affected by Alzheimer's disease than in normal brains. The present specification demonstrates that the C-terminal truncated forms of ApoE are present in plaques. Therefore, the antibodies of the claimed invention bind to ApoE in plaques. The bound antibodies would facilitate the destruction of the plaques as the plaques become coated with antibody, which will trigger direct destruction of the plaques by immune mechanisms such as complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC). For example, the antibody-coated plaques can be removed by phagocytosis, such as by internalization by microglia (see page 49, line 30, to page 50, line 19, of the specification).

Applicants' specification demonstrates that the antibodies that bind to ApoE-CTD were able to stimulate phagocytic uptake of CTD-bearing beads by human macrophage/microglia-like cells in a concentration-dependent fashion (see Example 32 at pages 78-79). Therefore, the present specification provides evidence that antibody binding to

ApoE-CTD in amyloid plaques would facilitate removal of the plaques. This working example is not contradicted by any evidence or reasoning provided in the Action.

Therefore, Applicants' specification discloses their invention in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

Withdrawal of the enablement rejections is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

*35 U.S.C. 101 –Utility*

Claims 1, 4, 11, 20-21, 28-32, 37-41, 51-55 and 59 were rejected as allegedly directed to nonstatutory subject matter. Adoption of the Examiner's suggestion to insert --isolated-- moots this objection. Withdrawal of the rejection is requested.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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## **Annex 1: Antibody Heavy and Light Chain Sequences**

### **Heavy Chain CDR3 sequences**

SEQ ID NO: 26	<b>Ser</b>	<b>Val</b>	<b>Leu</b>	<b>Leu</b>	<b>Asp</b>	<b>Tyr</b>
SEQ ID NO: 512	Xaa <sub>1</sub>	Xaa <sub>2</sub>	<b>Leu</b>	Xaa <sub>3</sub>	<b>Asp</b>	Xaa <sub>4</sub>
SEQ ID NO: 516	Gly	Xaa <sub>2</sub>	<b>Leu</b>	Xaa <sub>3</sub>	<b>Asp</b>	Xaa <sub>4</sub>
SEQ ID NO: 20	<b>Ser</b>	Xaa <sub>5</sub>	Xaa <sub>5</sub>	<b>Leu</b>	<b>Asp</b>	<b>Tyr</b>
SEQ ID NO: 23	<b>Ser</b>	<b>Leu</b>	<b>Asp</b>	<b>Leu</b>	<b>Asp</b>	<b>Tyr</b>
SEQ ID NO: 207	Gly	<b>Val</b>	<b>Leu</b>	<b>Asp</b>	<b>His</b>	<b>Tyr</b>
SEQ ID NO: 208	Gly	<b>Ile</b>	<b>Leu</b>	<b>His</b>	<b>Asp</b>	<b>Tyr</b>
SEQ ID NO: 209	Gly	<b>Val</b>	<b>Leu</b>	<b>Leu</b>	<b>Asp</b>	Lys
SEQ ID NO: 210	Gly	<b>Val</b>	<b>Leu</b>	<b>Phe</b>	<b>Asp</b>	Asn

Xaa<sub>1</sub> = **Ser** or Gly

Xaa<sub>2</sub> = **Val** or Ile

Xaa<sub>3</sub> = **Leu**, His or Phe

Xaa<sub>4</sub> = **Tyr**, Asn or Lys

Xaa<sub>5</sub> = any amino acid

### **Heavy Chain CDR2 sequence**

SEQ ID NO: 25 **Ser** **Ile** **Trp** **Pro** **Ser** **Gly** **Gly** **Gln** **Thr** **Trp** **Tyr** **Ala** **Asp** **Ser** **Val** **Lys**

### **Heavy Chain CDR1 sequence**

SEQ ID NO: 24 **Met** **Tyr** **Met** **Met** **Asp**

### **Light Chain CDR3 sequences**

SEQ ID NO: 35	<b>Leu</b>	<b>Gln</b>	<b>Tyr</b>	<b>Asp</b>	<b>Ser</b>	<b>Phe</b>	<b>Pro</b>	<b>Tyr</b>	<b>Thr</b>
SEQ ID NO: 269	Gln	<b>Gln</b>	<b>Tyr</b>	Lys	Thr	Tyr	<b>Pro</b>	<b>Phe</b>	<b>Thr</b>
SEQ ID NO: 275	<b>Leu</b>	<b>Gln</b>	Pro	Glu	Thr	Tyr	<b>Pro</b>	Trp	<b>Thr</b>
SEQ ID NO: 268	Gln	<b>Gln</b>	<b>Tyr</b>	<b>Asp</b>	Ala	<b>Phe</b>	<b>Pro</b>	<b>Phe</b>	<b>Thr</b>

### **Light Chain CDR2 sequences**

SEQ ID NO: 34	<b>Glu</b>	<b>Ala</b>	<b>Ser</b>	<b>Ile</b>	<b>Leu</b>	<b>Gln</b>	<b>Ser</b>
SEQ ID NO: 247	Gly	<b>Ala</b>	<b>Ser</b>	Thr	Val	<b>Gln</b>	<b>Ser</b>
SEQ ID NO: 252	His	<b>Ala</b>	<b>Ser</b>	Thr	<b>Leu</b>	<b>Gln</b>	<b>Ser</b>

### **Light Chain CDR1 sequences**

SEQ ID NO: 33	<b>Arg</b>	<b>Thr</b>	<b>Ser</b>	<b>Gln</b>	<b>Asp</b>	<b>Ile</b>	<b>Arg</b>	<b>Asn</b>	<b>His</b>	<b>Leu</b>	<b>Gly</b>
SEQ ID NO: 219	Gln	Ala	<b>Ser</b>	<b>Gln</b>	<b>Asp</b>	<b>Ile</b>	Ser	<b>Asn</b>	Tyr	<b>Leu</b>	Asn
SEQ ID NO: 226	<b>Arg</b>	Ala	<b>Ser</b>	Arg	Gly	<b>Ile</b>	<b>Arg</b>	<b>Asn</b>	Asn	<b>Leu</b>	Ala
SEQ ID NO: 218	<b>Arg</b>	<b>Thr</b>	<b>Ser</b>	<b>Gln</b>	<b>Asp</b>	<b>Ile</b>	Gly	<b>Asn</b>	<b>His</b>	<b>Leu</b>	Ala



# Heavy Chain Variable Region Sequences

SEQ ID NO: 40 (SEQ ID NOS: 24, 25 and 26 underlined)

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	<u>Met</u>	<u>Tyr</u>		
			20					25					30				
<u>Met</u>	<u>Met</u>	<u>Asp</u>	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ser	<u>Ser</u>	<u>Ile</u>	<u>Trp</u>	<u>Pro</u>	<u>Ser</u>	<u>Gly</u>	<u>Gly</u>	<u>Gln</u>	<u>Thr</u>	<u>Trp</u>	<u>Tyr</u>	<u>Ala</u>	<u>Asp</u>	<u>Ser</u>	<u>Val</u>		
	50					55				60							
<u>Lys</u>	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
65					70				75					80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90					95			
Ala	Arg	<u>Ser</u>	<u>Val</u>	<u>Leu</u>	<u>Leu</u>	<u>Asp</u>	<u>Tyr</u>	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr		
		100						105					110				
Val	Ser	Ser															
		115															

SEQ ID NO: 317 (SEQ ID NOS: 24, 25 and 208 underlined)

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	<u>Met</u>	<u>Tyr</u>		
			20					25					30				
<u>Met</u>	<u>Met</u>	<u>Asp</u>	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ser	<u>Ser</u>	<u>Ile</u>	<u>Trp</u>	<u>Pro</u>	<u>Ser</u>	<u>Gly</u>	<u>Gly</u>	<u>Gln</u>	<u>Thr</u>	<u>Trp</u>	<u>Tyr</u>	<u>Ala</u>	<u>Asp</u>	<u>Ser</u>	<u>Val</u>		
	50					55				60							
<u>Lys</u>	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
65					70				75					80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90					95			
Ala	Arg	<u>Gly</u>	<u>Ile</u>	<u>Leu</u>	<u>His</u>	<u>Asp</u>	<u>Tyr</u>	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr		
		100						105					110				
Val	Ser	Ser															
		115															

SEQ ID NO: 318 (SEQ ID NOS: 24, 25 and 209 underlined)

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	<u>Met</u>	<u>Tyr</u>		
			20					25					30				
<u>Met</u>	<u>Met</u>	<u>Asp</u>	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
			35				40					45					
Ser	<u>Ser</u>	<u>Ile</u>	<u>Trp</u>	<u>Pro</u>	<u>Ser</u>	<u>Gly</u>	<u>Gly</u>	<u>Gln</u>	<u>Thr</u>	<u>Trp</u>	<u>Tyr</u>	<u>Ala</u>	<u>Asp</u>	<u>Ser</u>	<u>Val</u>		
	50					55				60							
<u>Lys</u>	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
65					70					75				80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90					95			
Ala	Arg	<u>Gly</u>	<u>Val</u>	<u>Leu</u>	<u>Leu</u>	<u>Asp</u>	<u>Lys</u>	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr		
		100						105					110				
Val	Ser	Ser															
		115															

SEQ ID NO: 319 (SEQ ID NOS: 24, 25 and 210 underlined)

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	<u>Met</u>	<u>Tyr</u>		
			20					25					30				
<u>Met</u>	<u>Met</u>	<u>Asp</u>	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
			35				40					45					
Ser	<u>Ser</u>	<u>Ile</u>	<u>Trp</u>	<u>Pro</u>	<u>Ser</u>	<u>Gly</u>	<u>Gly</u>	<u>Gln</u>	<u>Thr</u>	<u>Trp</u>	<u>Tyr</u>	<u>Ala</u>	<u>Asp</u>	<u>Ser</u>	<u>Val</u>		
	50					55				60							
<u>Lys</u>	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
65					70					75				80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90					95			
Ala	Arg	<u>Gly</u>	<u>Val</u>	<u>Leu</u>	<u>Phe</u>	<u>Asp</u>	<u>Asn</u>	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr		
		100						105					110				
Val	Ser	Ser															
		115															

## Light Chain Variable Region Sequences

SEQ ID NO: 518 (SEQ ID NOS: 33, 34 and 35 underlined)

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Arg</u>	<u>Thr</u>	<u>Ser</u>	<u>Gln</u>	<u>Asp</u>	<u>Ile</u>	<u>Arg</u>	<u>Asn</u>	<u>His</u>
			20				25						30		
<u>Leu</u>	<u>Gly</u>	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Gln	Arg	Leu	Ile
	35						40					45			
Arg	<u>Glu</u>	<u>Ala</u>	<u>Ser</u>	<u>Ile</u>	<u>Leu</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Thr	Phe	Tyr	Gly
	50					55					60				
Ser	Gly	Tyr	Gly	Arg	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	<u>Leu</u>	<u>Gln</u>	<u>Pro</u>
65					70					75				80	
<u>Glu</u>	<u>Asp</u>	<u>Phe</u>	<u>Ala</u>	<u>Thr</u>	<u>Tyr</u>	Tyr	Cys	Leu	Gln	Tyr	Asp	Ser	Phe	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
105					110					115					

SEQ ID NO: 520 (SEQ ID NOS: 33, 34 and 35 underlined)

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Arg</u>	<u>Thr</u>	<u>Ser</u>	<u>Gln</u>	<u>Asp</u>	<u>Ile</u>	<u>Arg</u>	<u>Asn</u>	<u>His</u>
			20				25						30		
<u>Leu</u>	<u>Gly</u>	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
	35						40					45			
Tyr	<u>Glu</u>	<u>Ala</u>	<u>Ser</u>	<u>Ile</u>	<u>Leu</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	<u>Leu</u>	<u>Gln</u>	<u>Pro</u>
65					70					75				80	
<u>Glu</u>	<u>Asp</u>	<u>Phe</u>	<u>Ala</u>	<u>Thr</u>	<u>Tyr</u>	Tyr	Cys	Leu	Gln	Tyr	Asp	Ser	Phe	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
			100				105								

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SEQ ID NO: 43 (SEQ ID NOS: 33, 34 and 35 underlined)

Gln	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val
1				5					10					15	
Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Arg</u>	<u>Thr</u>	<u>Ser</u>	<u>Gln</u>	<u>Asp</u>	<u>Ile</u>	<u>Arg</u>	<u>Asn</u>
			20					25					30		
<u>His</u>	<u>Leu</u>	<u>Gly</u>	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Gln	Arg	Leu
	35						40					45			
Ile	Arg	<u>Glu</u>	<u>Ala</u>	<u>Ser</u>	<u>Ile</u>	<u>Leu</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Thr	Phe	Tyr
	50					55					60				
Gly	Ser	Gly	Tyr	Gly	Arg	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	<u>Leu</u>	<u>Gln</u>
65					70					75					80
<u>Pro</u>	<u>Glu</u>	<u>Asp</u>	<u>Phe</u>	<u>Ala</u>	<u>Thr</u>	<u>Tyr</u>	Tyr	Cys	Leu	Gln	Tyr	Asp	Ser	Phe	Pro
				85					90					95	
Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys				
			100					105							

SEQ ID NO: 295 (SEQ ID NOS: 219, 247 and 269 underlined)

Gln	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val
1				5					10					15	
Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Gln</u>	<u>Ala</u>	<u>Ser</u>	<u>Gln</u>	<u>Asp</u>	<u>Ile</u>	<u>Ser</u>	<u>Asn</u>
			20					25					30		
<u>Tyr</u>	<u>Leu</u>	<u>Asn</u>	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Gln	Arg	Leu
	35						40					45			
Ile	Tyr	<u>Gly</u>	<u>Ala</u>	<u>Ser</u>	<u>Thr</u>	<u>Val</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Arg	Phe	Ser
	50						55				60				
Gly	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln
65					70					75					80
Pro	Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	<u>Gln</u>	<u>Gln</u>	<u>Tyr</u>	<u>Lys</u>	<u>Thr</u>	<u>Tyr</u>	<u>Pro</u>
				85					90					95	
<u>Phe</u>	<u>Thr</u>	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Asp	Ile	Lys				
		100						105							

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**SEQ ID NO: 294 (SEQ ID NOS: 218, 34 and 268 underlined)**

Gln	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val
1				5					10					15	
Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Arg</u>	<u>Thr</u>	<u>Ser</u>	<u>Gln</u>	<u>Asp</u>	<u>Ile</u>	<u>Gly</u>	<u>Asn</u>
			20					25					30		
<u>His</u>	<u>Leu</u>	<u>Ala</u>	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Gln	Arg	Leu
	35						40					45			
Ile	Arg	<u>Glu</u>	<u>Ala</u>	<u>Ser</u>	<u>Ile</u>	<u>Leu</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Thr	Phe	Ser
	50					55					60				
Gly	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln
65					70					75					80
Pro	Glu	Asp	Phe	Ala	Ser	Tyr	Tyr	Cys	<u>Gln</u>	<u>Gln</u>	<u>Tyr</u>	<u>Asp</u>	<u>Ala</u>	<u>Phe</u>	<u>Pro</u>
				85					90					95	
<u>Phe</u>	<u>Thr</u>	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys				
		100						105							

**SEQ ID NO: 302 (SEQ ID NOS: 226, 252 and 275 underlined)**

Gln	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val
1				5					10					15	
Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	<u>Arg</u>	<u>Ala</u>	<u>Ser</u>	<u>Gln</u>	<u>Gly</u>	<u>Ile</u>	<u>Thr</u>	<u>Asn</u>
			20					25					30		
<u>Tyr</u>	<u>Leu</u>	<u>Ala</u>	Trp	Tyr	Gln	His	His	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu
	35						40					45			
Ile	Tyr	<u>His</u>	<u>Ala</u>	<u>Ser</u>	<u>Thr</u>	<u>Leu</u>	<u>Gln</u>	<u>Ser</u>	Gly	Val	Pro	Ser	Arg	Phe	Ser
	50					55					60				
Gly	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln
65					70					75					80
Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	<u>Leu</u>	<u>Gln</u>	<u>Pro</u>	<u>Glu</u>	<u>Thr</u>	<u>Tyr</u>	<u>Pro</u>
				85					90					95	
<u>Trp</u>	<u>Thr</u>	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys				
		100						105							

**Light Chain Constant Region Sequences**

**SEQ ID NO: 519**

Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
1				5					10					15	
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
			20					25					30		
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
		35					40					45			
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
	50					55					60				
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
65					70					75					80
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
				85					90					95	
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
			100					105							

**SEQ ID NO: 521**

Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
1				5					10					15	
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
			20					25					30		
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
		35					40					45			
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
	50					55					60				
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
65					70					75					80
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
				85					90					95	
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
			100					105							